UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/187,768	11/06/1998	ANTHONY H. CINCOTTA	2991/1B206-U	3476

7590 01/29/2002

DARBY & DARBY
805 THIRD AVENUE
NEW YORK, NY. 10022

EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/187,768	CINCOTTA ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-47,49-54,59 and 60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-47,49-54,59 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

The Amendment filed December 14, 2001 (Paper No. 17) in response to the Office Action of October 14, 2001 is acknowledged and has been entered. Claim 34 was amended. Claims 59 and 60 were added. (Applicant mistakenly numbered the new claims as Claims 55 and 56; however claims 55 and 56 were previously withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.) Thus, claims 34-47, 49-54, and 59-60 are pending and are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained

Claims 34-36,39, 43 and 49 remain rejected and new claim 59 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3,8, and 13 of U.S. Patent No. 5,792,748 in view of Werning et al. (Arch. Ontolaryngol. Head Neck Surg., July 1995, v121, pp. 783-789, IDS) and Cincotta et al. (Cancer Research, 1994, Vol. 54, pp. 1249-1258, IDS), as further evidenced by Molitch, ME (Endocrinol.Metab.Clin.North.Am., 1992, Vol. 21(4), Abstract only) for the reasons of record in Paper No. 15, pages 2-4.

Applicants argue (Paper No. 17, page 4) that the '748 patent does not contain any teaching or suggestion that neuroendocrine resetting therapy using a prolactin enhancer should be used in combination with PDT to arrest or eradicate tumors in a mammal. Applicants further argue that there is no hint in the patent that any benefit would be achieved with such a combination. This argument has been considered but is not found persuasive because applicant has reiterated what was known to be deficient in the claims of the '748 patent. This was previously detailed in Paper No. 15, page 3- *i.e.,* "US Patent No. 5,792,748 claims the above method, but does **not** include combining photodynamic therapy to eradicate the tumors." Furthermore, the disclosure of the '748 was never used against Applicant, rather claims 3, 8, 13 were the subject of obviousness-type double patenting since they are broadly drawn to inhibiting neoplastic growth via the administration of prolactin in a mammal. (Applicants have termed this neuroendocrine resetting therapy). Hence, applicants have first argued the merits of one reference without considering the combined teachings.

Applicant further argue (Paper No. 17, page 5) that the teachings of Werning *et al.* contain no disclosure or suggestion that a tumor bearing mammal be treated with the combination of PDT and neuroendocrine resetting therapy. Again, applicants have argued the reference individually and substituted the terminology "neuroendocrine resetting therapy" in exchange for what is actually claimed in the '748 patent- administering a prolactin enhancer. This is not found persuasive for the reasons above. Applicants further argue that the teachings of Werning *et al.* never suggest administering a prolactin enhancer to reset a daily prolactin rhythm, rather Werning *et al.* used the prolactin enhancer (metoclopramide) based on its "enhancement of DNA damage or increased blood flow and oxygen availability to the tumor".

Accordingly, applicants contend that the reference fails to disclose "any benefit or advantage" of combining PDT with the administration of a prolactin enhancer.

This argument has been considered but is not found persuasive. The fact that Werning *et al.* offers reasons why metoclopramide may enhance the effects of PDT would not preclude one of ordinary skill in the art from clearly comprehending the obvious synergism that occurs when PDT is combined with the prolactin enhancer. In fact, Werning *et al.* summarizes the motivation to combine by stating that the results "show that administering metoclopramide in combination with PDT may be a promising approach to the management of head and neck cancer" (Werning *et al.* , abstract). Hence, the fact that prolactin may have a direct effect on DNA does not render the combination of the references unobvious. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Finally, Applicant has clearly argued and discussed the references individually without addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981).

Applicants further argue that the Examiner has relied on an obvious to try standard (page 6) as the rationale for combining the cited references. This argument has been considered but is not found persuasive. The teachings of Werner *et al.* clearly suggest to one of ordinary skill a reasonable expectation of success because "tumors exposed to PDT alone showed 80% to 90% tumor regression with regrowth in most animals within 20 days"; however, "tumors treated with the prolactin enhancer plus PDT demonstrated 100% tumor regression without regrowth" (see Werning *et al.* , abstract). The above teachings further counter Applicant's showing of unexpected results (Paper No. 17, pages 6-9) because the suggested combination of the prior art also demonstrates an unexpected efficacy that would be achieved by combining neuroendocrine resetting therapy (i.e. the administration of a prolactin enhancer) and PDT. Thus, applicants arguments have not been found persuasive, and the rejection is maintained.

Claims 34-36,39, 43, 49, 59 remain directed to an invention not patentably distinct from claims 3,8, and 13 of commonly assigned U.S. Patent No. 5,792,748 for the reasons of record in Paper No. 15, page 4.

The assignee has not demonstrated that the conflicting inventions were commonly owned at the time the invention in this application was made.

Claims 34-47,49-54 remain rejected and new claims 59-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cincotta et al. (US Patent No. 5,792,748 and/or US Patent 6,071,914) in view of Werning et al. (Arch. Ontolaryngol. Head Neck Surg., July 1995, v121, pp. 783-789, IDS) and Cincotta et al. (Cancer Research, 1994, Vol. 54, pp. 1249-1258,

IDS), as further evidenced by Molitch, ME (Endocrinol.Metab.Clin.North.Am., 1992, Vol. 21(4), Abstract only) for the reasons of record in Paper No. 15, pages 7-9. Applicants traverse the obviousness rejection on the same grounds set forth above in regard to the obviousness-type double patenting rejections. These arguments have been considered but are not found persuasive for the reasons set forth above. Thus, applicants arguments have not been found persuasive, and the rejection is maintained.

Rejections Withdrawn

The rejection of Claims 34-35 and 43, 49 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 18 of U.S. Patent No. 6,071,914 in view of Cincotta et al. (Cancer Research, 1994, Vol. 54, pp. 1249-1258, IDS) and Lin, Chi-Wei (Cancer Cells, Vol. 3, No. 11, 1991, IDS) is withdrawn in view of applicants arguments there to.

NEW REJECTIONS

Claims 34-36,39, 43, 49, 59-**60** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3,**7**-8, 13, and of U.S. Patent No. 5,792,748 in view of Werning et al. (Arch. Ontolaryngol. Head Neck Surg., July 1995, v121, pp. 783-789, IDS) and Cincotta et al. (Cancer Research, 1994, Vol. 54, pp. 1249-1258, IDS), as further evidenced by Molitch, ME (Endocrinol.Metab.Clin.North.Am., 1992, Vol.

21(4), Abstract only). The rejection and reasoning remains the same as the above maintained obviousness-type double patenting rejection above except that claim 7 of the '748 patent is now included which essentially corresponds to newly added Claim 60 of the present application.

Accordingly, Claims 34-36,39, 43, 49, and 59-60 are directed to an invention not patentably distinct from claims 3,7-8, and 13 of commonly assigned U.S. Patent No. 5,792,748, for the reasons set forth previously and above.

Claims 34-37, 43, 49, and 59 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-13 and 28, 30 of U.S. Patent No. 6,071,914 in view of Werning et al. (Arch. Ontolaryngol. Head Neck Surg., July 1995, v121, pp. 783-789, IDS) and Cincotta et al. (Cancer Research, 1994, Vol. 54, pp. 1249-1258, IDS), as further evidenced by Molitch, ME (Endocrinol.Metab.Clin.North.Am., 1992, Vol. 21(4), Abstract only).

The pending claims are drawn to a method for arresting the growth of or eradicating tumors in a mammal bearing one or more tumors comprising comparing the daily plasma prolactin profile of said tumor bearing mammal to a normal daily prolactin profile for healthy mammals of the same species and sex; and adjusting the daily plasma prolactin profile of said tumor bearing mammal by administering a prolactin enhancer at appropriate time intervals of day such that the adjusted daily plasma prolactin profile of said tumor bearing mammal conforms to or approaches the normal daily plasma prolactin profile for healthy member so of the same species and sex of said mammal further comprising contacting the cells of said tumor with a

benzophenoxazine-analog photosensitizer having phototoxicity against tumor cells; and exposing said contacted tumor cells to light, such that the growth of said tumor is retarded or said tumor is eradicated (Claim 34); wherein said tumor bearing mammal is a human (Claim 35); wherein said prolactin enhancer is a member selected from the group consisting of melatonin (Claims 36-37); wherein said photosensitizer is selected from the group consisting of benzophenoxazine analogs (Claim 43); wherein benzophenoxazine analog is EtNBS (Claim 49).

Claims 12-13 of US Patent No. 6,071,914 are drawn to a method for treating a patient suffering from a neoplasm comprising comparing the blood prolactin level of said patient at each of a plurality of spaced apart time points during a 24-hour period to the corresponding prolactin level of a baseline prolactin profile for healthy humans of the same sex as said patient; adjusting the prolactin level of said patient to cause the patient's prolactin profile to approach or conform to the baseline prolactin profile by administering a prolactin reducer to said mammal at a predetermine time, thereby inhibiting the growth of said neoplasm in said human further comprising administering a prolactin enhancer to said patient (Claim 12); wherein said prolactin reducer is bromocriptine and said prolactin enhancer is melatonin (Claim 13).

Claims 28, 30 of US Patent No. 6,071,914 are drawn to a method for treating a patient suffering from a neoplasm comprising adjusting the prolactin level of said patient to cause the patient's prolactin profile to approach or conform to the baseline prolactin profile by administering a prolactin reducer to said patient at a predetermined time, thereby inhibiting the growth of said neoplasm in said human further comprising administering a prolactin enhancer to said patient (Claim 28); wherein said prolactin reducer is bromocriptine and said prolactin enhancer is melatonin (Claim 30).

The claims of US Patent 6,071,914 differ from the instant claims by not including photodynamic therapy equivalent to "contacting the cells of said tumor with a benzophenoxazine-analog photosensitizer having phototoxicity against tumor cells; and exposing said contacted tumor cells to light, such that the growth of said tumor is retarded or said tumor is eradicated (Claim 34); wherein said tumor bearing mammal is a human (Claim 35); wherein said prolactin enhancer is a member selected from the group consisting of melatonin (Claims 36-37); wherein said photosensitizer is selected from the group consisting of benzophenoxazine analogs (Claim 43); wherein benzophenoxazine analog is EtNBS" (Claim 49).

Werning et al. teach that combining PDT with a prolactin enhancer increases the percentage of tumor regression versus PDT alone (abstract). Metoclopramide, as evidenced by Molitch, ME is an prolactin enhancer.

Cincotta et al. teach that 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride (EtNBS), (a benzophenoxazine analog) is a unique photodynamic agent which inactivates solid tumors (page 1257) and that photodynamic therapy of EMT-6 tumors in mice with the 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride resulted in direct tumor cell killing (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Claims 12-13 and 28, 30 of US Patent 6,071,914 so as to add the step of photodynamic therapy because Werning *et al.* teach that photodynamic therapy (PDT) has emerged as a promising new modality for the treatment of cancer (page 748, 2nd column). Further, one would have been motivated to include PDT because Werning *et al.* specifically teach that the combination of PDT with the administration of a prolactin enhancer resulted in the increased regression of tumors versus PDT therapy alone. Furthermore, it would

have been obvious to substitute the photosensitizer used by Werning *et al.* (Werning *et al.* used a phthalocyanine- see abstract) with the benzophenoxazine analog (EtNBS) taught by Cincatta *et al.* because Cincatta *et al.* teach the advantages of using EtNBS over the porphyrin family- which includes phthalocyanines—in that in vivo studies indicate that unlike the porphyrin derivatives, the benzophenoxazine analogues seem to rapidly accumulate intracellularly and cause tumor destruction with minimal damage to the vasculature (see pages Cincatta *et al.*, page 1250, 1st column, 1st paragraph, and page 1249, 2nd column, 2nd paragraph). Thus, clearly, the combined teachings suggest to one of ordinary skill in the art a reasonable expectation of success in arresting the growth of or eradicating tumors by combining PDT with the administration of a prolactin enhancer.

Claims 34-37, 43, 49, and 59 are directed to an invention not patentably distinct from claims 12-13 and 28, 30 of commonly assigned U.S. Patent No. 6,071,914 for the reasons above.

Commonly assigned U.S. Patent No. 6,071,914 discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g).

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
January 24, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600